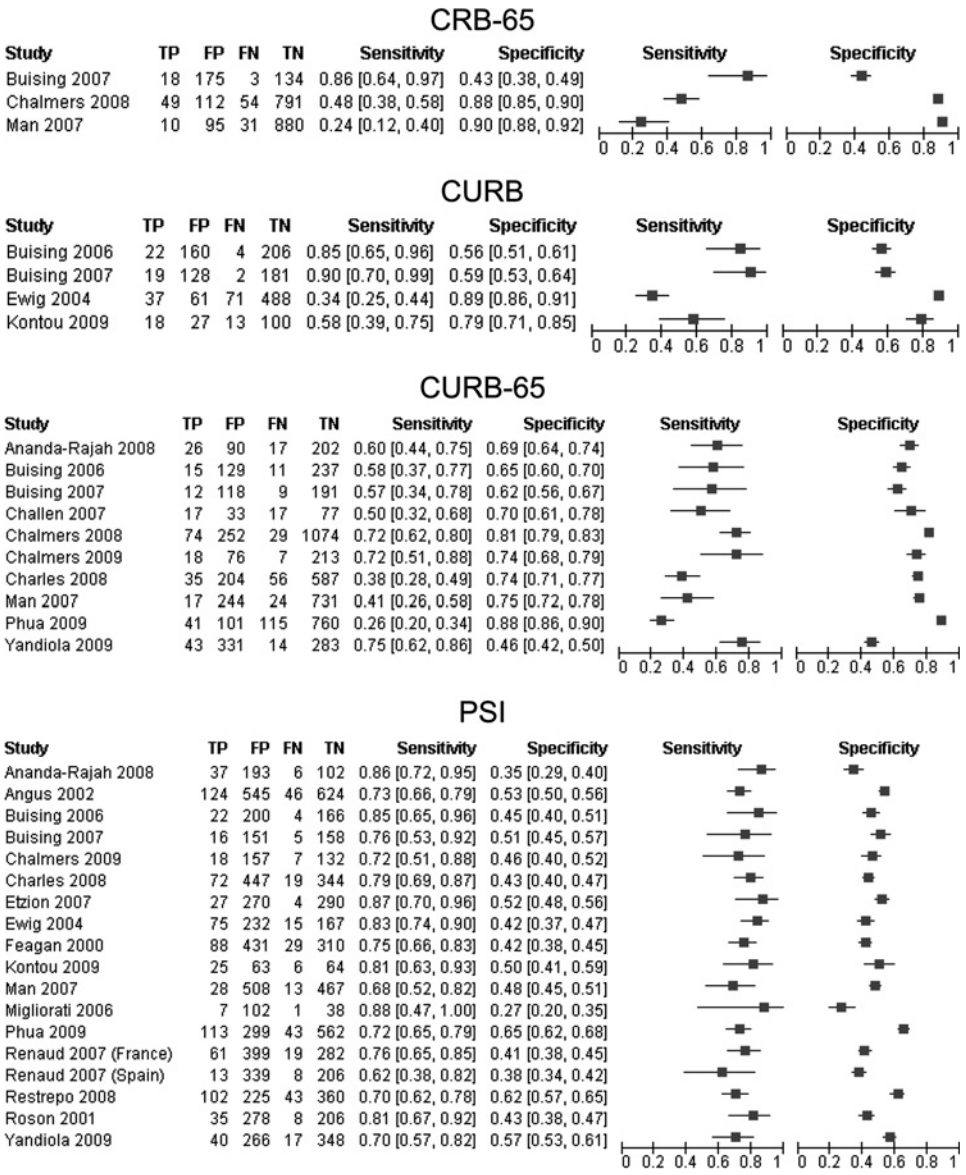

Figure 1 Forest plots of sensitivity and specificity. PSI, pneumonia severity index.

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Authors' response

We thank Dr Challen for her letter regarding our article[1 2] in which she highlights the limitations of CURB65 and PSI for guiding ICU admission. This is an important point which a number of authors including ourselves have made previously.[3] Our meta-analysis demonstrates that CURB65 and PSI predict 30-day mortality, the end-point for which these scores were originally derived. Unfortunately, 30-day mortality risk does not translate directly into management decisions and so it is important to establish whether severity scores can impact positively in clinical practice. This 'impact analysis' is a critical part of the validation of all prognostic tools.[4]

Guidelines based on severity scores significantly increase the proportion of low-risk patients treated in the community without compromising patient safety or satisfaction[5], and we have recently shown that guidance of antibiotic prescribing using CURB65 can safely reduce broad-spectrum antibiotic use.[6] For critical care admission, however, the role of severity scores is not established. The major indications for critical care unit admission are requirement for mechanical ventilation or vasopressor support. As others have said, these patients are generally not difficult to identify[7] and there are established guidelines such as surviving sepsis for the identification and management of these critically ill patients. There is little evidence that simply being managed on an intensive care unit for a patient not requiring mechanical ventilation or vasopressors improves outcome. Use of scoring systems such as CURB65/PSI or other recently proposed scores to admit these patients to critical care lacks evidence of benefit and may be impractical.

Studies suggest that less than 10% of hospitalised patients with CAP are currently admitted to ICU's. Implementing scoring systems would require a massive expansion of scarce ICU resources. Admitting all patients with CURB65 ≥3 (17–42% of patients), PSI class V (average of 20.9% of patients), SMART-COP score ≥3 (43.3% of patients in the derivation study) or all patients with three or more IDSA-ATS criteria (26% of patients based on the study of Phua *et al*)[8] is not going to be possible

without a huge expansion of critical care beds that could not be justified without evidence of benefit to patients. It should be noted that most of the studies reported by Dr Challen failed to exclude patients with do not attempt resuscitation orders or with directives not to be admitted to the ICU. Therefore, these percentages and the pooled performance characteristics do not necessarily reflect their 'real life' clinical utility.

Expanding on Dr Challen's statement that application of these tools 'should be with caution', we would suggest that severity scores should only be used to predict outcomes for which they have been validated and, as suggested by McGinn,[4] scoring systems should have their impact assessed in clinical studies before being applied to guide clinical decisions.

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Exit of leucocytes across the alveolar epithelium worsens lung injury

Persson and Uller are to be commended for their review highlighting the important role of leucocyte egression in the resolution of airway inflammation.[1] They go on to speculate that egression across the alveolar epithelium may be detrimental, because, unlike for the airways, there is no mucociliary escalator, and luminal cells that are not removed will interfere with gas exchange. They allay this concern citing work from Cory *et al*[2] using a mousemodel of asthma. In this model a deficiency of matrix metalloproteinase (MMP)-2 and/or MMP-9 inhibits leukocyte egression across the airway epithelium and leukocytes accumulate in the interstitium around the bronchial wall. The MMP-2/MMP-9 knock-out (KO) mice died from asphyxia (presumably from bronchoconstriction). The wild type (WT) mice survive with less peribronchovascular inflammation, but more mild diffuse alveolar inflammation than the KOs.[2]

Persson and Uller present this as evidence that egression into the alveolar airspace, as for the airway lumen, may also be beneficial. But it would be dangerous to extrapolate this to other inflammatory diseases for two reasons. First, the leucocytes may have reached the alveolar space not by crossing the alveolar epithelium, but from overspill of the exuberant egression into the airway lumen. Second, in the asthma model described death is by bronchoconstriction and modest alveolar inflammation may be tolerated. In addition, the hazards of egression have been convincingly demonstrated in a murine model in which bleomycin inhalation is used to induce alveolar (rather than airway) inflammation.[3]

Li and colleagues found that MMP-7 deficiency was protective against death following bleomycin lung injury. They went on to show, very elegantly, that MMP-7 is required to establish the chemoattractant gradient that drives leucocyte egression across the alveolar wall.[3] The protective effect of the MMP-KO was reversed when n-formyl-nle-leu-phe (nFNLP) was instilled with bleomycin, and egression of leucocytes into the alveolar airspace was re-established.[3]

There is still much to be learnt about egression, and in particular the complex regulation and interplay of extravasation and egression in inflammation and resolution of disease. Our own research examines the molecular differences involved in egression across distinct epithelial barriers (alveolar vs bronchial), with a view to enhance the transepithelial exit of leucocytes across the bronchial epithelium (beneficial) while limiting their exit across the alveolar epithelium (detrimental).[4] The ability to differentially alter the exit of leucocytes across distinct epithelial barriers may be essential when designing drugs and biological compounds to enhance the resolution of inflammation.

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Authors' response

We obviously agree with Porter[1] on the need to make a distinction between egression of infiltrated leucocytes across mucosal epithelia, where a swift further elimination of the lumen cells can be expected to occur (nasal, tracheobronchial, gut, bladder), and the bronchiolar–alveolar epithelial linings where there is a risk of undesirable accumulation of lumen cells. We repeat this cautionary note in an extended review on resolution of cell-mediated respiratory diseases where we discuss a role of egression in the elimination not only of granulocytes and lymphocytes but also of mast cells and dendritic cells.[2] We further discuss how elimination of leucocytes through egression can be compatible with the use of sputum cell counts to adjust treatment in asthma.[1] The concept developed in our two reviews is underpinned foremost by clinical observations and experimental findings in patients. We were indeed surprised to find that numerous, human, so far little understood, in vivo data supported the resolving role of transepithelial egression whereas little support for the role of leucocyte apoptosis, the accepted paradigm, emerged. However, Porter's comments mainly concern mouse model findings. Of interest are supporting findings in murine (mouse and rat) models of 'asthma' indicating that inhibition of egression can have serious respiratory consequences. We are aware of severe limitations of mouse models[3] but felt that these data should be discussed. We also speculated that cell traffic in mouse airways, better than cell activation, could be relevant. However, the distinction between bronchial and